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Derivations of Ethylenetetracarboxylic Acid

DERIVATIVES OF ETHYLENETETRACARBOXYLIC ACID

BY

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY

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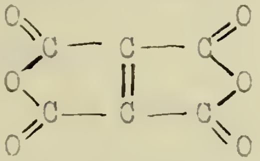
INTRODUCTION

Although the tetraethyl ester has been known for some time, ethylenetetracarboxylic acid was first prepared by Bischoff and Siemaszko[1] in 1896, who were interested in the product formed when the acid was heated. Normally, one of two things might be expected. It might lose two molecules of water and give the anhydride,



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which would be a new oxide of carbon. Or it might lose two molecules of carbon dioxide to give maleic or fumaric acid. These investigators found that on slow heating, carbon dioxide was lost with the formation of fumaric acid. On rapid heating, however, dimethyl maleic anhydride was formed by the union of two molecules of the acid with a loss of six molecules of carbon dioxide and one of water.

This thesis is a description of attempts to prepare the above oxide of carbon and other derivatives of ethylenetetracarboxylic acid.

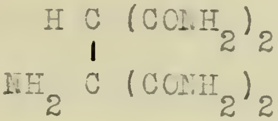
HISTORICAL PART

The tetraethyl ester of ethylenetetracarboxylic acid was first prepared in 1883, by Conrad and Guthzeit[2] from chloromalonic ester and sodium in anhydrous ether. Bischoff and Rach[3] prepared it about a year later from di-sodium malonic ester and iodine. Blank and Sampson[4] obtained a better yield by refluxing bromo-malonic ester in dry benzene with anhydrous potassium car-

bonate.

The tetra-methyl ester was prepared in 1896 by Bischoff[5] by heating the tetra methyl ester of acetylenetetracarboxylic acid, $C_2H_2(CO_2CH_3)_4$, with bromine. Later[6], he prepared ethylenetetracarboxanilide by refluxing the tetra-methyl ester with aniline. This is a very insoluble compound, melting at 270° C.

Scholl, Holdermann, and Langer[7] have found that the tetra-ethyl ester with alcoholic ammonia gives the tetramide of asparagine dicarboxylic acid,



$$\begin{array}{l} \mathrm{H\ C\ (CONH_2)_2} \\ \quad\ | \\ \mathrm{NH_2\ C\ (CONH_2)_2} \end{array}$$

Philippi and Uhl[8] believe that the course of this reaction is first, addition of ammonia to the double bond and then the formation of the tetra amide.

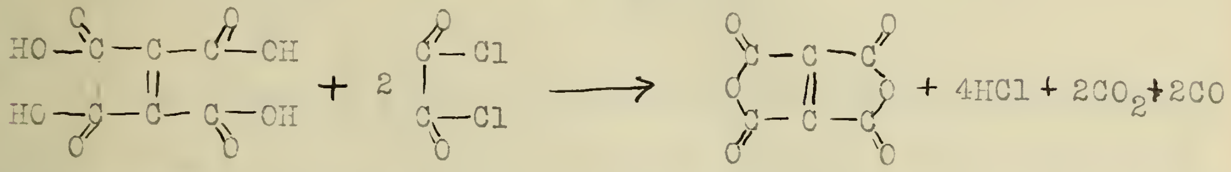
The tetra-potassium salt[1] of the acid can be prepared by the saponification of the ester with concentrated potassium hydroxide. If a solution of the tetra-potassium salt is acidified with acetic acid, the di-potassium salt is formed[9]. The calcium and silver salts are insoluble in water. The zinc salt is soluble.

The free acid was prepared in 1896 by Bischoff and Siemaszko[1], from the di-potassium salt. The finely powdered salt was suspended in dry benzene and treated with dry hydrochloric acid gas. The acid was obtained by filtering off the benzene and extracting the solid residue with absolute ether.

THEORETICAL PART

Since ethylenetetracarboxylic acid on heating loses carbon dioxide, instead of merely losing two molecules of water to form

the anhydride, it is evident that chemical methods must be employed to prepare the oxide C_6O_6. Oxalyl chloride would seem to be the most promising reagent for this purpose. The reaction would be expected to take place as follows:



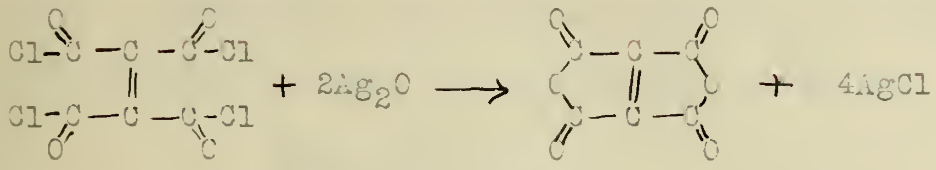
It was found, however, that even long refluxing with an excess of oxalyl chloride left the acid unchanged. Thionyl chloride is another reagent of the same type, but this too, had no effect on the free acid. Acetic anhydride decomposed the free acid to give a black solution from which nothing could be isolated. Acetyl chloride decomposed the acid slightly, but some was recovered unchanged.

In many cases, it is possible to prepare the anhydride of an aicd from the alkali salts by the use of oxalyl chloride. However, the di-potassium salt of this acid on treatment with oxalyl chloride does not yield the anhydride[10]. The use of thionyl chloride also failed to give results. Acetyl chloride and acetic anhydride with the tetra-potassium salt failed to yield the oxide.

The tetra acid chloride of the acid can be prepared by the action of phosphorous pentachloride on either the free acid or the di-potassium salt. This is a very reactive light yellow liquid. It hydrolizes rapidly in the air to reform the acid, and it reacts vigorously with absolute alcohol. It is soluble in the common organic solvents.

It might be expected that an extremely reactive acid chloride,

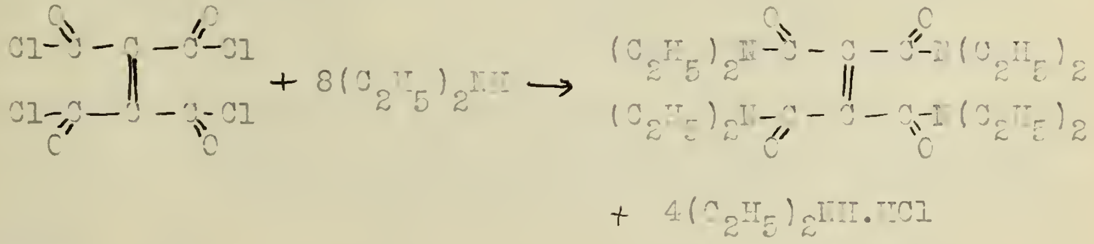
such as this one, would react with silver oxide to give silver chloride and the anhydride according to the equation,



It was found on trial, that succinic anhydride could easily be made from succinyl chloride by this method. With the tetra-acid chloride, however, the product was silver chloride, and the silver salt of the acid. This was probably due to either or both of two reasons. Succinyl chloride is known to exist in two tautomeric forms

and it may have been the second form which reacted, while the tetra-acid chloride may not have the unsymmetrical form. Or the fact that the tetra-acid chloride contains a double bond may make it more difficult to close the ring.

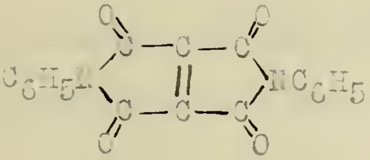
The tetra-acid chloride reacts with diethylamine to give the tetradiethylamide of the acid.



This forms white crystals which are soluble in water, alcohol, benzene, ether, and chloroform. The compound can be recrystallized from petroleum ether.

On adding the acid chloride dissolved in absolute ether to

an excess of aniline, a light yellow insoluble substance is formed. After recrystallization from oxalic ester, it melts at 220°-224° C. According to Bischoff[5], the tetra anilide melts at 270° C. The compound isolated here may be the diphenyl imide,



Owing to a lack of time, not enough of this substance was obtained for analysis.

EXPERIMENTAL PART

Bromomalonic Ester.

This was prepared by the method of Knoevenagel[11], with a slight modification. 1000 grams of malonic ester were placed in a five liter flask fitted with a stirrer, a dropping funnel, and a reflux condenser. The malonic ester was heated to about 50 on a steam cone, and 1025 grams of bromine were added in the course of six or eight hours with constant stirring. The temperature was kept near 50 by regulating the steam and the rate of flow of the bromine. When all the bromine had been added, the flask was heated to the full temperature of the steam cone until no more hydrobromic acid was evolved. The flask was removed from the steam cone and suction applied over night. The product was then vacuum distilled. Boiling point 135°-150° at 25 mm. Yield 1250 grams or 83.5%.

Tetra-ethyl-ester of Ethylenetetracarboxylic Acid.[4]

400 grams of bromomalonic ester were dissolved in 1500 cc. of dry benzene and placed in a 5 liter flask fitted with a stirrer, reflux condenser, and a wide tube through which potassium carbonate

could be added. 200 grams of anhydrous potassium carbonate were added, and the mixture was then refluxed on the steam cone with stirring. Carbonate was added in 200 gram portions at intervals of 2-3 hours until a total of 1400 grams had been added. The refluxing and stirring was continued for a total of 30-36 hours. The mixture of potassium carbonate and bromide was filtered off, and the benzene distilled on the steam cone. The residue was distilled in a vacuum. Boiling point 190°-210° C at 8 mm. Yield 160 grams, or 60.5%.

Saponification of the Tetra Ester.

100 grams of tetra ester were gradually added to a hot solution of 150 grams of potassium hydroxide in 150 cc. of water. The tetra-potassium salt separated out even before cooling. After cooling, alcohol was added until no more salt precipitated, and after standing a short time, the crude salt was filtered off, and washed with a little alcohol. This can be purified further by dissolving it in the smallest possible volume of water, filtering off any insoluble material, and reprecipitating, and washing with alcohol as before. Yield 103 grams, or 91.5%.

In most cases, however, the crude tetra-potassium salt was converted into the di-potassium salt by making a concentrated solution, filtering, and adding acetic acid to acid reaction. After cooling alcohol was added until precipitation was complete, and the salt filtered off, and washed with a little alcohol and ether. Yield 83 grams, or 93.5% (from 100 grams of tetra ester).

Ethylenetetracarboxylic Acid.

20 grams of finely powdered tetra-potassium salt were suspend-

ed in anhydrous benzene. Dry hydrochloric acid was passed through the mixture with thorough shaking. The benzene was filtered off, and the residue washed with a little dry benzene and then extracted with hot absolute ether. On evaporating the ether, the acid was obtained in white crystals. Yield 8.2 grams, or 71.5%. Bischoff and Siemaszko[5] used the di-potassium salt and obtained 80% yield.

Attempts to Prepare the Oxide, C_6O_6.

Effect of Various Reagents on the Free Acid.

Oxalyl Chloride: 2.7 grams of oxalyl chloride were added to 2 grams of acid suspended in 5 cc. of dry benzene, and the mixture refluxed three hours on a steam bath. At the end of this time, the acid was filtered off unchanged. In another attempt, 3 grams of acid dissolved in absolute ether and 5 grams of oxalyl chloride were refluxed for 5 hours. Some of the solution was evaporated and the unchanged acid was recovered. About 10 more grams of oxalyl chloride were then added to the remaining solution which was then refluxed 24 hours. On evaporation of the ether the residue was identified as the original acid by means of a mixed melting point determination.

Thionyl Chloride: 5 grams of acid, after refluxing for 23 hours with 30 grams of thionyl chloride were recovered unchanged.

Acetyl Chloride: 5 grams of acid were refluxed for one hour with an excess of acetyl chloride. On vacuum distillation, 2-3 cc. of acetic anhydride were obtained. A tarry residue in the flask contained some unchanged acid.

Acetic Anhydride: 2 grams of acid on refluxing with an excess

of acetic anhydride gave a brownish black solution which gave tar on vacuum distillation.

Effect of Certain Reagents on the Salts of the Acid.

Thionyl Chloride: 22 grams of di-potassium salt were refluxed with 110 grams of thionyl chloride for one hour. The liquid became brown and after filtering of the unchanged salt, and evaporating the thionyl chloride in a vacuum, a small amount of liquid residue remained. This charred and decomposed when an attempt was made to vacuum distil it.

Acetic Anhydride: 20 grams of tetra-potassium salt were refluxed 2 hours with 120 grams of acetic anhydride. The acetic anhydride was filtered off, and the residue extracted with hot glacial acetic acid. On cooling, crystals separated. These were recrystallized from glacial acetic acid, after which they melted at 145°-147° C. They contained potassium and corresponded to potassium acid acetate, $KH(C_2H_3O_2)_2$.

Acetyl Chloride: 20 grams of finely powdered tetra-potassium salt suspended in dry benzene were treated with 10 grams of acetyl chloride, and refluxed 3 hours. The benzene was filtered off, and the residue was extracted with absolute ether. On evaporation of the ether, a very small amount of ether soluble material remained. There was not enough to determine it's nature. The ether insoluble part was unchanged tetra-potassium salt.

Attempts to Prepare the Anhydride from the Acid Chloride.

Succinyl Chloride: 27 grams of succinic acid and 100 grams of phosphorous penta-chloride were mixed in a flask and allowed to stand over night. The liquid was then filtered through glass wool, and vacuum distilled. Boiling point 120°-128° at 90 mm.

Yield 30 grams, or 85%.

Succinic Anhydride: 15 grams of dry silver oxide were added to 3 grams of succinyl chloride in dry chloroform. A vigorous reaction took place causing the chloroform to boil. The hot solution was filtered off, and on evaporation, it left white needles, which melted at 114°-118°, without further purification. (Succinic anhydride melts at 119.6° C).

Tetra Acid Chloride of Ethylenetetracarboxylic Acid.

18.5 grams of acid were gradually added to 100 grams of phosphorous penta-chloride and allowed to stand over night. The liquid was filtered through glass wool, and vacuum distilled. Boiling point 118-122 at 17 mm. Yield 17.8 grams, or 70.5%. The product was redistilled and analyzed, but the results were always too low. This was due to the extreme ease with which the compound hydrolyzes back to the acid, thus losing hydrochloric acid.

The same compound was prepared by gradually mixing 50 grams of di-potassium salt with 180 grams of phosphorous penta-chloride and allowing the mixture to stand over night. It was then thoroughly extracted with absolute ether. The solution was then vacuum distilled. Boiling point was 135°-142° at 38 mm. Yield 3[illegible] grams, or 60%.

These two methods of preparation together with the fact that the chloride is hydrolyzed to the acid, leave no doubt as to the identity of the compound. The chloride has been described in the theoretical part.

Effect of Silver Oxide on the Acid Chloride.

8 grams of silvef oxide were added to 2 grams of the tetra acid chloride dissolved in dry chloroform. A reaction took place,

though it was much less vigorous than in the case of succinyl chloride. The mixture was heated to boiling on a hot plate, and then filtered hot. On evaporation of the chloroform, an oily residue, which had the odor of the acid chloride remained. This was dissolved in more chloroform and then refluxed with more Ag_2O for two hours. It was then filtered and evaporated again. This time a small amount of white solid residue remained, which was found to be silver chloride.

The experiment was repeated using ether instead of chloroform, but with no better results. In this case, the silver oxide was afterwards extracted with hot water. On cooling and standing, a slight silver color appeared. This was in all probability due to the solution of a small amount of the silver salt of the acid.

On repeating the experiment an excess of the acid chloride was used. 9.6 grams of silver oxide were added to a solution of 12 grams of the acid chloride in absolute ether. The mixture was refluxed over night, and on filtering and vacuum distilling, 6 grams of acid chloride were recovered. After distillation of the acid chloride, a tarry residue remained in the flask. This resulted from something which was formed during the reaction, as the acid chloride can be redistilled with very little decomposition. It was impossible to isolate anything which resembled an acid anhydride from the ether insoluble part.

Derivatives from the Tetra Acid Chloride.

With Diethyl Amine: 10 grams of tetra acid chloride dissolved in absolute ether were slowly added to 22 grams of diethyl amine in ether. The precipitate of diethyl amine hydrochloride was

filtered off, and washed in absolute ether. The ether was evaporated from the filtrate and the residue distilled in a vacuum. Boiling point, 243°-247° at 28 mm. Yield 10 grams, or 65.5% The distillate solidified, giving a straw colored solid. For analysis, the substance was recrystallized twice from petroleum ether, and dried in a vacuum desiccator over NaOH. This gave white crystals melting at 70°-71°. The compound is soluble in all the common solvents, such as water, alcohol, ether, benzene, and chloroform. It has a slightly bitter taste.

Analysis gave the following results.

.2500 grams required 23.16 cc. N/10 HCl		
Calculated for $C_{22}H_{40}O_4N_4$	N	13.20 per cent
Found		12.96 per cent

Derivative from Aniline: 1 gram of tetra cid chloride dissolved in dry ether was added to an excess of aniline in ether. The precipitate was filtered off, and washed with alcohol, water and then alcohol again followed by a little ether. The substance remaining on the filter paper was recrystallized from oxalic ester, and then melted at 215°-217° C. On account of a lack of time, not enough for analysis could be prepared. The substance was insoluble in all the common solvents. It probably was a diphenyl imide.

Notes

1. Bromomalonic ester prepared in the manner described, and also when it was washed before dsitillation often had a very pungent odor, and gave off fumes which had a lachrimatory effect. In other cases, the odor was pleasant. This was probably due to the use of different grades of malonic ester, some of it probably

containing some cyanacetic ester.

2. It seems probable that the tetra ester can be prepared from bromomalonic ester by the use of a small amount of sodium hydroxide, instead of a large excess of potassium carbonate, but the details have not been completely worked out.

3. In all cases in the experiments described, where hygroscopic or easily hydrolyzable materials were refluxed, the condenser was closed with a calcium chloride tube.

SUMMARY

A large number of attempts were made to prepare the oxide C_6O_6, but all were unsuccessful.

Two new derivatives of ethylenetetracarboxylic acid were prepared and identified. These were the tetra acid chloride, and the tetra diethyl amide.

An aniline derivative was prepared, but not identified.

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II

O-ETHERS OF β PHENYLHYDROXYL-AMINE

O-ETHERS OF PHENYLHYDROXYL AMINE

INTRODUCTION and HISTORICAL

It has been shown[1] that β phenyl-hydroxyl-amine will rearrange to p-aminophenol under the influence of acids. In the presence of alcohol and sulfuric acid, a good yield of p-phenetidine is obtained, together with some o-phenetidine and azoxybenzene.[2] The reaction to give phenetidine could take place in two ways. The rearrangement might take place first giving aminophenol, which would then be ethylated by the alcohol and sulfuric acid. Or, it is possible that ethylation with the formation of an o-ether of β phenylhydroxyl amine is the first step, with the rearrangement coming second. Since these ethers are unknown, attempts were made to prepare several members of the series in order that their reactions, and rearrangements could be studied.

Bamberger[3] and his students have made numerous attempts to prepare members of this class of compounds, but they have thus far been unsuccessful. They employed methyl iodide, or bromide, under varied conditions and obtained azoxybenzene, azobenzene, aniline, and methyl aniline. Hydrolysis of N-benzoyl β phenylhydroxyl-amine and o-methyl ether failed to give the desired result. With methyl sulfate, they obtained a small amount of reddish-brown oil, which they thought contained the o-methyl ether, but it was impossible to purify it. The full details of these investigations are not available at the present time.

THEORETICAL PART

One would expect that the sodium salt of β-phenylhydroxylamine would react with alkyl halides to give the O-ethers. It

was found, however, that when the sodium salt was treated with methyl or ethyl iodide, azo or azoxybenzene was formed. The procedure was then somewhat modified. An excess of the iodide was added to a dry ether solution of the β phenylhydroxylamine. Finely divided sodium was then added until the vigorous reaction stopped. The mixture of sodium and sodium iodide was filtered off, and the solution evaporated. This left a reddish-brown oil which was probably identical with that obtained by Bamberger and his pupils[3]. This oil decomposed on distillation at 2 mm. pressure.

Since the compounds could not be distilled, attempts were made to prepare solid members of the series. p-chloro- and p-bromo-phenylhydroxylamines were used, in hopes that they might give a solid ether. It was found, however, that these gave the corresponding azo and azoxy derivatives even more easily than the unsubstituted compound.

It is possible that a positively substituted compound, such as p-methyl β phenylhydroxylamine would not give the azo and azoxy compounds so easily, but the research was discontinued at this point.

EXPERIMENTAL PART

β Phenylhydroxylamine Sodium Salt.

A dry ether solution of β phenylhydroxylamine was prepared by dissolving the product obtained by the method of Marvel and Kamm[5], in alcohol, free ether, and drying the solution with anhydrous sodium sulfate. Finely divided sodium was added to the dry solution until the reaction was complete. The suspension of the sodium salt was then separated from the excess sodium by decantation. The yield was not determined since it was necessary to keep the

salt under ether to prevent decomposition.

Sodium Salt with Ethyl Iodide.

Some of the sodium salt suspended in ether was refluxed a short time with an excess of ethyl iodide. On filtering and evaporating a few crystals of azoxybenzene were obtained. When the experiment was repeated with larger amounts, a small amount of a reddish-brown oil and some azobenzene were obtained. The oil was probably the same as that which Bamberger mentioned[3].

With a modified procedure the oil was prepared in larger yield. A dry solution of 50 grams of β phenyl-hydroxylamine was mixed with 250 grams of ethyl iodide. Finely divided sodium was added with cooling until the vigorous reaction was over. The sodium and sodium iodide was filtered off, and the solution evaporated. This left a reddish-brown oil similar to the one obtained by using the sodium salt. On attempting to distill the oil at 60 mm., it decomposed giving azoxybenzene and other products, which were not identified. This experiment was repeated except that a pressure of 4 mm. was used, but the oil still decomposed at 80 C. Enough heat was liberated in the decomposition to cause the thermometer in the distilling flask to register 50-80 higher than the one in the oil bath in which the flask was heated.

When ethyl iodide was replaced by methyl iodide, the results were the same. In one case, a pressure as low as 2 mm. was used, but decomposition still took place. In all cases, the decomposition started slowly when the thermometer in the oil bath registered about 80°C. It gradually became more vigorous as heat was liberated, until finally the whole mass frothed and boiled.

The above clearly shows that the ethers cannot be distilled

and in hopes of preparing a solid derivative the following experiments were carried out.

Chloro-β phenylhydroxylamine with Sodium and Ethyl Iodide.

This compound was prepared by the method of Bamberger and Baudisch[6]: 5 grams were dissolved in ether and the solution dried with anhydrous sodium sulfate and then filtered. An excess of ethyl iodide was added, and the solution was then treated with finely divided sodium. Filtration and evaporation yielded p-chloroazoxybenzene.

p-Bromophenylhydroxylamine was prepared by the same method and on treatment with ethyl iodide and sodium gave p-bromoazoxybenzene.

These experiments were repeated a number of times, but no different results were obtained, and the work was discontinued.

SUMMARY

An oil was obtained which was probably β phenylhydroxylamine O-ether, but it could not be purified by distillation at low pressures. Azoxybenzene could be easily isolated from the decomposition products.

Attempts to prepare solid members of the series were likewise unsuccessful, the product being mainly azoxybenzene derivatives.

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